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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
MAYER, SUZANNE MARIE	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 11/03/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/789,428	VLODAVSKY ET AL.	
	Examiner	Art Unit	
	Suzanne M. Mayer, Ph.D.	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 February 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 112, 2nd paragraph

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claim 14 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The limitation of contacting heparanase with an inhibitory effective amount of eosinophils under suitable conditions is indefinite. What actually constitutes "suitable conditions" include a large number of conditions which are going to differ dramatically when carrying out the method step, for instance, *in vivo* vs *in vitro*. Furthermore, each of these different processes are going to have its own particular suitable conditions which have been left undefined and have no art acceptable meaning.

3. Claim 34 recites the limitation "The use according to claim 32....". There is insufficient antecedent basis for this limitation in the claim because claim 32 is a method claim.

4. Claim 34 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is indefinite because the recitation of "wherein said composition is as defined in claim 5", however, the claim depends from claim 32 which is dependent upon claim 1. Therefore which composition this instant claim is actually

intending as a limitation to the claim is unclear. Is it the composition of claim 1 or is it the pharmaceutical composition of claim 5?

5. Claims 30-37 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: the actual steps involved in the preparation of a composition. The claims instead cite method steps of an intended use of the composition, not the actual preparatory steps involved in making the composition.

6. Claims 1-37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims are rejected because the limitation set forth includes major basic protien. MBP is naturally produced as a pre-pro-MBP protein that is 225 amino acids long, with the pre part being defined as a signal sequence of 15 amino acids, the pro part being defined as a highly acidic 90 amino acid region, and the rest of the MBP protein being a highly cationic 117 amino acid protein. It is the 117 residue MBP protein which elicits the cytotoxic activity which it is well known for and recognized for in the art. However, it unclear whether all of these various forms of MBP are included in the claims. Further, the inhibition of heparanase with MBP, to which all of the claims are drawn, is not known in the art. Therefore, it is entirely unclear what part of the major basic protein inhibits heparanase, as stated in the claims, the pre-pro-MBP protein, the pro-MBP protein, just the MBP protein or all of them.

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

This is the first of three enablement rejections:

7. Claims 1-5, 7-8, 14, 16, 18-19, 20, 22-23, 29-3 and 35-37 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. In the instant case the claims are drawn to any functional fragment of any of the three eosinophil secondary granules basic protein (e.g. major basic protein (MBP), eosinophil cationic protein (ECP), eosinophil derived neurotoxin (EDN) or eosinophil peroxidase (EPO)).

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single,

simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

In the instant case the quantity of experimentation would be large since there are myriad fragments to choose from and no way to know which ones will be functional without testing each and every one. The amount of guidance in the specification is zero with regard to fragments having some activity other than the enzymatic activity of the entire protein and there is no recitation of any essential or conserved structure or sequences that may be essential to produce a functional fragment for these three proteins. No working examples are present of functional fragments. The nature of the invention is such that many fragments of many different lengths may or may not have biological activity and in this case in particular there may be no way to test for any particular activity. The state of the prior art is that many biological activities exist that might be possessed by various peptides. The relative level of skill in this art is very high. The predictability as to what fragment will have which activity is zero. The claim reads on fragments from a di-peptide up to one amino acid less than the full-length proteins.

When the factors are considered in their entirety, the Wands analysis dictates a finding of undue experimentation and thus, the claim is not enabled.

This is the second of three enablement rejections:

8. Claims 3, 5-28, and 35-36 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to the inhibition of heparanase glycosidase activity which includes pathologic disorders include carcinoma, melanomas, leukemia and lymphoma (see specification, p. 8, paragraph [00027]) in a sufficient amount of eosinophil cell lysate, any one of the eosinophil secondary granule basic protein or any functional fragment thereof, poly-L-arginine and any combination thereof, for the inhibition to occur. Thus a skilled artisan would be required to perform experimentation such that it would be undue experimentation, especially since this inhibitory effect of heparanase with the claimed compositions is not known in the prior art.

The factors to be considered in determining whether undue experimentation is required are summarized above in paragraph 8. Undue experimentation would be required because the quantity of experimentation required to test every single one of the claimed inhibitors and the combinations thereof would be substantial and the amount of guidance given in the specification void of any help in determining what an effective

amount would be for even a single one of the claimed ingredients of the composition. There is a single working example for MBP, ECP, EDN and EPO, used separately and not in combination in an *in vitro* experiment (see Figure 5) but no other functional fragments thereof, fusion proteins, a nucleic acid construct encoding the protein(s), a host cell expressing said construct, a cell, a cell line and tissue endogenously expressing the protein(s) which specify how much or what concentrations are effective in inhibiting heparanase activity. The nature of the invention is such that it is non-trivial and requires considerable experimentation because each separate protein and each combination thereof is going require a different concentration for inhibition to occur. The state of the prior art does not aid or direct one of ordinary skill in the art because it is not known in the art that eosinophil granules basic proteins are inhibitors of heparanase activity. The relative skill of those in the art is high yet one in the art would still require assistance and detailed guidance to make and/or use the claimed invention without undue experimentation. The predictability of what concentrations are effective is zero and the claim limitations are an open invitation for experimentation.

When the factors are considered in their entirety, the Wands analysis dictates a finding of undue experimentation and thus, the claims are not enabled.

This is the third of three enablement rejections:

9. Claims 16 and 20-28 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to

which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to methods of treating a subject in need thereof by inhibiting heparanase glycosidase activity by administering an effective amount of any one of eosinophil secondary granules protein, which includes major basic protein (MBP). It is well documented and known in the art that eosinophils are cytotoxic. For example, Furuta et al. describe eosinophils as such, "Eosinophils normally reside in tissues with mucosal surfaces such as the gastrointestinal tract. A variety of inflammatory and allergic diseases, including inflammatory bowel disease (IBD), parasitic infections, eosinophilic gastroenteritis, asthma, atopic dermatitis, and allergic rhinitis are associated with increases in the number of eosinophils within affected tissues". Thus how the administration of cytotoxic proteins to a subject which will not elicit an inflammatory immune system response while still functioning to inhibit heparanase glycosidase activity is unclear because the concentration necessary for inhibition of a heparanase glycosidase activity may exceed the lowest levels of detection in the subject.

The factors to be considered in determining whether undue experimentation is required are summarized above in paragraph 8. The quantity of testing in order to determine if administration of a pharmaceutical composition that comprises, for example MBP, and whether or not the concentration that is administered to a subject not only inhibits heparanase activity but also elicits an adverse and negative immune response in the patient is considerable because the use of this protein for this heparanase effect

has never been considered in the prior art. The only examples in the prior art are drawn to methods of inhibiting eosinophils and the immune response that they cause, and not to administering them. The specification does not even address this issue what so ever so there is zero guidance in how a skilled artisan should have to deal with such a situation. The only working example present is drawn to administration of MBP in a mice, but again it is not addressed what the appropriate protocol might be to avoid an adverse immune response. Further, it seems that no testing was done on this matter in the mice which were administered MBP. The nature of the invention is such that it may put subjects at risk for adverse immune responses which may be lethal to some. The relative skill of those in the art is exceedingly high and the predictability of whether the administration of the composition will adversely affect the subjects due to an inflammatory immune response is huge.

When the factors are considered in their entirety, the Wands analysis dictates a finding of undue experimentation and thus, the claim is not enabled.

This is the first of two written description rejections:

10. Claims 1-5, 7-8, 14, 16, 18-19, 20, 22-23, 29-3 and 35-37 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

In the instant case the claims are drawn to any functional fragment of any of the three eosinophil secondary granules basic protein (e.g. major basic protein (MBP), eosinophil cationic protein (ECP), eosinophil derived neurotoxin (EDN) or eosinophil peroxidase (EPO)). The claims do not require that the functional fragments of the proteins possess any particular conserved structure or other disclosed distinguishing features other than being functional. Thus, the claims are drawn to an undefined genus of amino acids with the only potential to recognize them being by sequence identity or hybridization ability.

To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factors present in claims is the partial structure of several different proteins. There is not even identification of any particular portion of the structures which might be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description.

Vas-Cath Inc. V. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed."* The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented

what is claimed." As discussed above, the skilled artisan cannot envision the detailed structures of functional fragments of MBP, EPO, EDN and/or ECP, and therefor conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the methods of making the claimed invention. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating or making it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

This is the second of two written description rejections:

11. Claims 3, 5-28, and 35-36 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The claims are drawn to the inhibition of heparanase glycosidase activity which includes pathologic disorders include carcinoma, melanomas, leukemia and lymphoma (see specification, p. 8, paragraph [00027]) in a sufficient amount of eosinophil cell lysate, any one of the eosinophil secondary granule basic protein or any functional fragment thereof, poly-L-arginine and any combination thereof, for the inhibition to occur.

Examples of *in vitro* inhibition of heparanase is given in figure 5, and the effective concentrations also stated for MBP, EPO, EDN and ECP. However, no examples for poly-L-arginine, the effective of amount used for eosinophil lysates in figure 5, or any combinations of MBP, EPO, ECP, and EDN functional fragments thereof, a fusion protein, a nucleic acid construct encoding the protein, a host cell expressing said construct, a cell, a cell line and tissue endogenously expressing the protein(s). Thus it is unclear how applicant was in possession of the invention as claimed when the working examples are limited to MBP, EPO, and ECP, separately and not in combination with one another.

Vas-Cath Inc. V. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed."* The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." As discussed above, the skilled artisan cannot envision the amount sufficient to inhibit heparanase glycosidase activity when using functional fragments of MBP, ECP or EPO, a fusion protein, a nucleic acid construct encoding the protein, a host cell expressing said construct, a cell, a cell line and tissue endogenously expressing the protein(s) and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the methods of making the claimed invention. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating

or making it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

Claim Rejections - 35 USC § 102

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claims 1-13 are rejected under 35 U.S.C. 102(a) as being anticipated by Davis et al. Davis et al. disclose a pharmaceutical composition containing EDN, ECP, MBP and EPO which is used to test the lower limits of detection on the skin for a subjects inflammatory immune response reaction. Thus the limitations of the claims have been met.

14. Claims 1-3 are rejected under 35 U.S.C. 102(b) as being anticipated by Futura et al. Futura et al. disclose a composition of major basic protein (MBP). Since a composition claimed as such is not limited except that it must contain at least MBP, then the purification protocol and protein that comes off a Sephadex-column at the end step is still a composition. Thus Futura et al., disclose a composition of MBP in 0.025 M acetate buffer at pH 4.3 and 0.15 M NaCl. Thus the limitations of the claims as stated have been met.

Conclusion

16. No claim is allowed.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Suzanne M. Mayer, Ph.D. whose telephone number is 571-272-2924. The examiner can normally be reached on Monday to Friday, 8.30am to 5.00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SMM
28 October, 2004

ROBERT A. WAX
PRIMARY EXAMINER
Art Unit 1653